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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/588,458
Filing Date: August 04, 2006
Appellant(s): MATHEUS ET AL.

Anthony J. Zelano
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 8/19/09 appealing from the Office action mailed 6/11/09.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

GROUNDS OF REJECTION NOT ON REVIEW

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

The following grounds of rejection have not been withdrawn by the examiner, but they are not under review on appeal because they have not been presented for review in the appellant's brief.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 5-10 and 12-17 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13, 15-24 and 26-27 of copending Application No. 10/996,597 in view of US 6,171,586 ('586). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a liquid formulation of EGFR antibody, including cetuximab. 10/996,597 ('597) in claim 21 recites a concentration up to 50 mg/ml, which is highly concentrated (see claims 2-3 of the instant application). Claim 19 of '597 is drawn to making the stable antibody formulation using tangential flow filtration, which is a type of ultrafilatration (see instant specification at page 7, lines 24-25). The instant claims do not recite the inclusion of a buffer, amino acid and surfactant in the formulation.

US 6,171,586 teaches a stable aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody not subjected to prior lyophilization, a buffer maintaining the pH in the range from about 4.5 to about 6.0, a surfactant and a polyol, along with uses for such a formulation (see Abstract). Further disclosed is that one or more other pharmaceutically acceptable carriers, excipients or stabilizers may be included in the formulation provided, such as additional buffering agents, antioxidants, and methionine (see column 23). Also disclosed is a list of buffers including citrate, acetate, histidine (an amino acid), and succinate (see column 22, lines 18-30). The polysorbates surfactants disclosed are a family of surfactants which include, polysorbates 20 (col. 22, lines 49-52). '586 also discloses sodium chloride as a tonicifier that may stabilize the antibody (see Column 22-23). Stability for at least one month at room temperature is disclosed (col. 6, lines 1-2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the aqueous solution disclosed in '586 to further stabilize the liquid formulation claimed in the instant application. One would have been motivated to do so with a reasonable expectation of success by the teachings of '586 for increased stability for an aqueous preparation of an antibody suitable for therapeutic use.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16 and 21 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16 and 21 recite the limitation "claim 7". There is insufficient antecedent basis for this limitation in the claims. Claim 7 has been cancelled.

Claim 21 is also indefinite because it recites "an additional medicament active ingredient", however, it is unknown what the intended activity is. Therefore, the metes and bounds of the claim are not clear.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,252,055	RELTON	6-2001
WO 02/096457	ARVINTE ET AL.	12-2002

Sridhar et al., "Inhibitors of epidermal-growth-factor receptors: a review of clinical research with a focus on non-small-cell lung cancer" The Lancet Oncol. vol. 4, no. 7 (Jul 2003), pp. 397-406.

Stites et al., Basic & Clinical Immunology, 8th Ed., Norwalk CT:Appleton & Lange (1994), p. 317.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the

obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 8, 11, 17 and 22-24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sridhar et al. (Lancet Oncol., 4(7): 397-406, July 2003) and WO 02/096457 A2 for the reasons set forth in the previous Office action (repeated below).

Sridhar et al. teaches (two paragraph beginning p. 398 col. 2 with the second full paragraph) that:

> Monoclonal antibodies have been developed that target different members of the EGFR superfamily. They are highly specific with few side-effects and may be synergistic with chemotherapy and radiation….
>
> Cetuximab (IMC-C225) is a human-murine chimeric IgG monoclonal antibody that competitively binds to the extracellular domain of EGFR.... Preclinical studies show that cetuximab inhibits the proliferation of cell lines expressing EGFR and increases the cytotoxic activity of chemotherapy and radiation. Cetuximab alone and in combination with chemotherapy or radiotherapy was generally well tolerated in phase I trials.... Cetuximab in combination with chemotherapy has shown activity in head and neck and colorectal cancers with acceptable toxic effects.

Sridhar et al. also discuss other EGFR antibodies in clinical trials as cancer therapies, including EMD72000 (Table 1 and p. 400, col. 1, first full paragraph). Sridhar et al. do not discuss antibody formula concentration or the means of concentrating an antibody formulation.

WO 02/096457 teaches highly concentrated formulations of antibodies with concentration of at least 50 mg/ml up to 250 mg/ml and methods of making them by ultrafiltration (p. 4, first and second full paragraphs and, *e.g.*, p. 22, first full paragraph). The desirability of the antibody formulation is stated (p. 2, middle): "Thus, there is a demand on the market for stable, liquid, injectable antibody formulations; and, in particular, for highly concentrated stable liquid, injectable antibody formulations. There is also a need for stable aqueous solutions comprising a high concentration of antibody protein that can be used as a starting material or intermediate in process to obtain stable liquid antibody formulations of the invention." The advantage of highly concentrated formulations being suitable for pre-filled delivery devices because of the small volume needed is also discussed (p. 7, first full paragraph).

Additionally taught is that the antibodies may be monoclonal, including chimeric antibodies which are humanized, antibody fragments and antibody derivatives which are PEGylated (p. 9, first full paragraph through p. 10, first full paragraph). Excipients for the formulations are disclosed (*e.g.*, middle of p. 13).

It would have been obvious to the artisan of ordinary skill at the time the invention was made to have cetuximab or other EGFR antibody in clinical trials (monoclonal and/or humanized, including EMD72000) as described by Sridhar et al. in a highly concentrated formulation because WO 02/096457 teach the demand on the market for one that can be injectable and/or can serve as a starting material or intermediate to obtain a suitable therapeutic formulation. It would have been obvious to use ultrafiltration as a means of concentrating the antibody formulation because WO 02/096457 teaches that this part of a general method for preparation of high concentrated liquid formulations.

(10) Response to Argument

Appellants argue (first full paragraph of p. 5 of brief) that "An aspect of the present invention is directed to the preparation of highly concentrated, liquid formulations of Mab c225 and Mab h425 as stable, ready-to-use solutions having low viscosity, low application volumes… and that are applicable for subcutaneous administration." However, "Preparations of highly concentrated, liquid formulations of antibodies are afflicted with technical challenges and routine protocols for protein concentration are not always applicable for large proteins with specific properties, such as, monoclonal antibodies that are usable in the clinical setting." Appellants assert that for any given antibody, especially for a monoclonal antibody, a specific method has to be developed to attain a highly concentrated formulation thereof. The core three-dimensional conformation must remain intact with functional groups being protected from degradation [citing Lam et al. (US 6,171,586)]. "To this end, it was also recognized that monoclonal antibodies poses a difficult problem with respect to high concentrations, especially if pharmaceutically critical stabilizers should be omitted." (emphasis added by Appellants) The argument has been fully considered, but is not persuasive. It is noted that no claim has a limitation addressing the viscosity of liquid formulation nor presence of "stabilizers". WO 02/096457, relied upon in the

rejection, reduced to practice the purification and high concentration liquid formulation of an IgE antibody, which is structurally similar to an IgG antibody but has an additional H chain domain (Stites et al., Basic & Clinical Immunology, 8th ed., Norwalk, CT:Appleton & Lange, (1994) p. 317, Fig. 24-2, presented only for factual information), making it at least structurally, equivalently complex compared to a typical monoclonal antibody. While the preferred embodiment is an anti-IgE antibody (p. 10, second full paragraph), there was no limitation on the type of antibody for which the concentrating process may be used. At the bottom of page 18 in WO 02/096457 it is stated, "The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention." Example 7, for example, is entitled "General method for the preparation of high concentrated liquid formulations." It simply requires "a solution of purified antibody" and provides E25 as a non-limiting example. Further, claim 1 is drawn to a stable aqueous solution comprising an antibody at a concentration at least 50 mg/ml, without limitation on type of antibody. Claim 28 is an example of a process for the preparation of a therapeutic liquid formulation wherein the generic antibody is concentrated to more than 150 mg/ml. Additionally, as stated on page 6 of the previous Office action mailed (3/19/09), "WO 02/096457 discloses concentration methods for antibodies, including monoclonal antibodies. For the method, the particular specificity of the antibody is unimportant. The use of a prior art anti-EGFR antibody such as cetuximab in the method of WO 02/096457 where the exemplary antibody was an IgE antibody is a case in which the artisan of ordinary skill would have recognized the substitution of one known antibody for another yielding predictable results."

Appellants cite (p. 5 of brief toward the end of the first full paragraph) *In re Hedges*, 783 F.2d 1038, 228USPQ 685 (Fed. Cir. 1986) as discussed in MPEP § 2145 for the statement that, "proceeding contrary to accepted wisdom in the art is evidence of non-obviousness." This has been fully considered, but does not affect the finding the obviousness. The Examiner maintains that the prior art taught highly concentrated liquid antibody formulation and that references neither teach away from the instant invention nor support the instant invention as having proceeded contrary to the accepted wisdom of the prior art for the reasons set forth in the rejection and as discussed above and in previous Office actions.

Appellants argue (sentence bridging pages 5-6 of brief) that prior art relied upon does not provide motivation for "a skilled worker to choose precisely Mab c225 or Mab h425 and combine it with precisely the generic process of concentrating proteins, especially since the details and examples of the secondary reference would point particularly to methods of concentrating other types of antibody molecules." Example 1 of WO 02/096457 is cited (p. 6 of Brief) as using omalizumab, an anti-IgE antibody, which it is argued is not equivalent to c225 or h425 monoclonal antibodies claimed in the instant invention which *"specifically* bind EGFR with high binding-affinity." (emphasis added by Appellants) "More specifically, neither Sridhar nor Arvinte provides any hint or suggestions that the specific-epitope binding antibodies of the present invention (i.e., Mab c225 or Mab h425) can be prepared as highly concentrated formulations (50 mg/ml to 180 mg/ml). Without such motivation, there can be no obviousness. *In re Baird*, 16 F.2d 380 (Fed. Cir. 1994)." The argument has been fully considered, but is not persuasive. As discussed in the first paragraph of this section, WO 02/096457 (Arvinte) does teach a general method of making highly concentrated antibodies in liquid formulation, whether the antibody is an IgE or an IgG monoclonal antibody. Again, though the exemplary antibody was an IgE antibody, one of ordinary skill in the art would have had a reasonably expectation of successfully using the method with the c225 antibody (cetuximab) of Sridhar because IgE and IgG antibodies are structurally and functionally similar. It would have been obvious to use an antibody with therapeutic benefit because WO 02/096457 explicitly presented a "General method for the preparation of high concentrated liquid formulations" and specifically stated that the antibody used in accordance with the present invention may be monoclonal (*e.g.*, p. 9, 3rd full paragraph). Additionally, the reference noted therapeutic advantages of highly concentrated liquid antibody formulations for pre-filled delivery devices (p. 7, first full paragraph), as well as market demand for "stable, liquid, injectable antibody formulations; and, in particular, for highly concentrated stable liquid injectable antibody formulations" (p. 2, middle). Because at least two anti-EGFR antibodies, Mab c225 and EMD72000, were in clinical trials for cancer treatment and Mab c225 had been shown to have the potential of synergistic activity with chemotherapy and radiation as disclosed by Sridhar, one of ordinary skill in the art at the time in instant invention was made would have been motivated to use Mab c225 and any other anti-EGFR antibody with clinical relevance in a highly concentrated liquid formulation as taught by WO 02/096457 with a

reasonable expectation of success. The importance of Mab c225 in the treatment of at least head and neck and colorectal cancers (see Sridhar et al., p. 399, middle of col. 1) would have made it an obvious choice for concentrating for injectable liquid formulation.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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